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Journal Pre-proof

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PII: S2667-1026(21)00086-3
DOI: https://doi.org/10.1016/j.imed.2021.09.001
Reference: IMED 25

To appear in: *Intelligent Medicine*

Received date: 20 July 2021
Revised date: 15 September 2021
Accepted date: 29 September 2021

Please cite this article as: Zhenxing Xu , Chang Su , Yunyu Xiao , Fei Wang , AI for COVID-19: Battling the pandemic with computational intelligence, *Intelligent Medicine* (2021), doi: https://doi.org/10.1016/j.imed.2021.09.001

Review

AI for COVID-19: Battling the pandemic with computational intelligence

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Abstract

The new coronavirus disease 2019 (COVID-19) has become a global pandemic leading to over 180 million confirmed cases and nearly 4 million deaths until June, 2021, according to the World Health Organization. Since the initial reported from December 2019 in Wuhan, China, COVID-19 has demonstrated a high transmission rate (with a R0 > 2), a diverse set of clinical characteristics (e.g., high rate of hospital and intensive care unit admission rates, multi-organ dysfunction for critically ill patients due to hyperinflammation, thrombosis, etc.), and tremendous burden on health care systems around the world. To understand the serious and complex disease and develop effective control, treatment, and prevention strategies, researchers from different disciplines have been making significant efforts from different aspects including epidemiology and public health, biology and genomic medicine, as well as clinical care and patient management. In recent years, artificial intelligence (AI) has been introduced into the healthcare field to aid clinical decision-making for disease diagnosis and treatment such as detecting cancer based on medical images and has achieved superior performance in multiple data-rich application scenarios. In the COVID-19 pandemic, AI techniques have also been used as a powerful tool to overcome the complex disease. In this context, the goal of this study is to review existing studies on applications of AI techniques in combating the COVID-19 pandemic. Specifically, these efforts can be grouped into the fields of epidemiology, therapeutics, clinical research, social and behavioral studies and are summarized. Potential challenges, directions, and open questions are discussed accordingly, which may provide new insights into addressing COVID-19 pandemic and would be helpful for researchers to explore more related topics in the post-pandemic era.

Keywords: **COVID-19 pandemic; Artificial intelligence; Electronic health record; Machine learning**

1.Introduction

The unprecedented outbreak of new coronavirus disease 2019 (COVID-19) has put people around the world at risk. The COVID-19 pandemic originated from Wuhan, China, in December 2019 and spread throughout other countries of the world quickly because of a high transmission rate (with R0 value bigger than 2) [1]. The scarcity of resources and the worry of overburdened healthcare systems has impelled majority governments to restrict traveling or lockdown cities [2]. The COVID-19 pandemic has caused over 180 million confirmed cases and nearly 4 million deaths until June 2021, according to the World Health Organization [3]. Scientists have identified genome sequence of the virus and asserted it to be a member of the β-CoV genera of the coronavirus family [4], which can attack human respiratory system, cause fever, cough, and other flu-like symptoms, and further affect multiple tissues and organ systems [5]. In addition, patients with COVID-19 may rapidly develop serious dysfunctions and even critical illness, leading to a suddenly boosted requirement of hospital beds, mechanical ventilation devices, and critical patient care resources [6]. Therefore, there is an urgent need for new technologies to help clinicians and health care providers to address this worldwide health crisis.

Artificial intelligence (AI), advanced by the rapid development of computer hardware and software and mathematics, is a wide range of techniques that allow computers thinking and working like human brain to support decision making. AI techniques, especially the machine learning (ML) and deep learning (DL), have demonstrated superior performance in many real-world data applications ranging from computer vision to natural language processing. In recent years, AI techniques have also been introduced into the healthcare field and lead to a new route to effectively derive knowledge in terms of disease conditions from complex health data to improve human health care, such as clinical decision-making [7-8]. In COVID-19, the increasing availability of diverse types of data makes it promising to apply AI techniques to assist us to overcome the pandemic [9]. In this context, significant efforts that used AI to address COVID-19 have been drawn from different perspectives, including epidemiology and public health, biology and genomic medicine, as well as clinical care and patient management, etc. In this study, we discussed the applications of AI that mainly focused on ML and DL techniques in COVID-19.

There are several previous studies in terms of using AI for fighting COVID-19 [10-14]. They generally have a specific focus on AI's applications in epidemiology and therapeutics in COVID-19. Muhammad et al. [11] surveyed 35 studies on the use of AI in COIVD-19 diagnosis, epidemic forecasting, and patient management. Hussain et al. [12] focuses on big data, Internet of Things (IoT), AI, cloud computing techniques in fighting against the COVID-19 pandemic. In addition, Pham et al. [13], Chen et al. [14] and Nguyen et al. [10] also discussed the use of AI in vaccine and drug development. Compared to the previous studies, we considered a broader spectrum of application areas of AI in fighting against the pandemic, including epidemiology, therapeutics, clinical research, social and behavioral studies. In each field, we review existing studies and detail how the AI techniques advanced COVID-19 study, but also discuss unsolved issues and challenges as well as potential opportunities of AI in this field which may provide insights for researchers to bridge the gap between the application of AI and health care in the pandemic. The overall framework of this review is shown in **Figure 1**.

References for this Review were found through searches of PubMed, Scopus, Google Scholar, and Web of Science for papers. Keywords include "COVID-19" "SARS-CoV-2", "non-pharmaceutical public health interventions", "epidemic control", "drug repositioning", "drug repurposing", "network medicine", "machine learning", "artificial intelligence", "convolutional neural networks", "deep learning", "subphenotyping", "misinformation", "social media", "health impacts", "public health", and "mental health". The titles and abstracts were furtherly checked for inclusion. Some relevant papers were also collected from the review of citations referenced. Most of the reviewed articles were published after June 2020. To clearly summarize these articles, we grouped them into four categories according to the types of applications, including (1) epidemiology, (2) therapeutics, (3) clinical research, (4) social and behavioral studies.

2. AI in COVID-19 Epidemiology

AI models have been involved in the epidemiology studies, mainly focusing on the COVID-19 trend prediction. In particular, the involved AI models include data-driven-based statistical models, epidemiology-based compartment models, and individual-based agent models and hybrid models.

2.1 Data-driven-based statistical models

The data-driven-based statistical models mainly include regression-based parametric or non-parametric models such as Auto-Regressive Integrated Moving Average (ARIMA), Support Vector Regression (SVR), Random Forest (RF), deep learning (DL) model like Recurrent Neural Network (RNN), and so on. For example, Parbat and Chakraborty [15] used the SVR model to predict the COVID-19 trend to the total number of deaths, recovered cases, cumulative number of confirmed cases, and number of daily cases using the Johns Hopkins epidemiological data [16]. The proposed model was efficient and presented higher accuracy than linear or polynomial regression methods. While building a predictive model for COVID-19 trend forecasting, these pure data-driven-based statistical models typically only considered building relationships between a dependent variable such as the number of deaths and independent variables such as the number of days, but didn't explicitly consider the epidemiological characteristics of the infectious disease.

2.2 Epidemiology-based compartment models

The aim of compartment models is to divide entire populations into multiple different compartments (i.e., states) such as susceptible, exposed, infectious and recovered, and then apply ordinary differential equations (ODEs) to model the transitions among these compartments. Two popular compartment models including Susceptible-Infected-Resistant (SIR) [17] and Susceptible-Exposed-Infected-Removed (SEIR) [18] are used to model the spread of infectious disease in terms of multiple previous epidemic outbreaks such as SARS [19] and the ongoing COVID-19 [20-21]. Compared to data-driven-based statistical models, the compartment models were built on the well-established mathematical/physical laws, which consider the epidemiological characteristics of infectious disease and there is an assumption for the compartment models that the counts observed from these compartments have the potential to reflect reproduction numbers. Compartment models are still the mainstream approach in epidemiological research of infectious disease [22]. However, determination of parameters of the traditional compartment models are difficult and usually rely on predefined hypotheses. The use of AI techniques has shown their strength in estimating the optimal parameters of the compartment models, and hence led to a new way to improve the compartment models in COVID-19 trend prediction [23-24].

2.3 Individual-based agent models and hybrid models

Recently, several researchers have utilized fine-grained methods to model a population through agent simulation for COVID-19 trend prediction [25-26]. An individual based agent model is to simulate a real environment in an abstract representation to estimate the spread of epidemic diseases, which has three main elements including the agent (e.g., person), the factors of each agent (e.g., age), and the links between agents. Adel Alzu'bi et al. [26] used an individual based agent model to simulate the spread of COVID-19 in an urban area by considering multiple agent factors including age, gender, smoking status and isolation tendency. They found that the non-pharmaceutical public health interventions, such as staying home, hospital isolation policies, and preventing travel between cities, made contributions to the reduction of the prevalence and the deaths in COVID-19 pandemic.

In addition, some hybrid models such as the combination of mechanistic disease transmission model and a curve-fitting model [27] and the combination of RNN model and susceptible-infected (ISI) model [24], have been used in the COVID-19 trend prediction. These hybrid models mainly considered the combination in terms of epidemiology model and ML techniques, which not only capture the epidemiological characteristics of infectious disease but also enhance the ability of building the relationships between input data and output data by pure data-driven method. The epidemiology model in a hybrid model is usually used to obtain information related to COVID-19 trends such as infection rates, which are utilized as input features for the AI prediction model. The hybrid models have also showed great promise to accelerate the COVID-19 trend prediction.

2.4 Challenge and opportunities

From the above summary, we can observe that multiple AI-based epidemiology models have been used to predict the spread of COVID-19 and obtain some promising initial results. However, there remain several challenges and opportunities for the improvement of predictive performance. Specifically,

(1) The spread of infectious disease like COVID-19 is usually complex and influenced by multiple factors such as population density, demographic composition, weather conditions, non-pharmaceutical public health interventions, medical resource disparities, city traffic flows and so on [28-32]. Researchers need to consider how to combine these factors and set different weights for them. Investigating the impact of individual factors on the spread of COVID-19 trend is also an interesting topic.

(2) The epidemiology-based compartment models are sensitive to the initial values of model parameters such as infectious population, hospitalized population, and dead population. The determination of initial values of these parameters is usually based on the public reported data (including confirmed cases and recovered cases). However, the reported cases may not be very correct and usually much less than their real numbers because of multiple kinds of reasons such as the test capability [33]. Although integrating data-driven machine learning methods can relieve the dependence of initial values and improve the predictive performance, the regular (weekly or daily) updating for AI models to reflect changing dynamics is challenging because of more and more confirmed cases that need more train time.

(3) The mutations of COVID-19 have been found [34], which were more transmissible. The mutated viruses may have higher fatalities, which influence the patterns of the spread of infectious disease. Incorporating mutation when building predictive models for the COVID-19 trend is important [35] but rarely discussed.

(4) Building hybrid models by combining multiple predictive models is a good method for improving accuracy of predictive models. However, most previous hybrid COVID-19 trend predictive models mainly use the output of one model as the input feature of another model. Building a voting mechanism from many different predictive models would be beneficial for the predictive performance.

3. AI in COVID-19 therapeutics: Drug discovery

There are two common strategies for development of drugs to treat diseases including traditional drug development (de novo drug discovery) and drug repurposing [36]. The traditional drug development method usually starts from building novel chemical compounds based on molecular units and needs multiple steps including preclinical research, safety review, clinical study, FDA review, and FDA postmarket safety monitoring, which usually take more than 10 years and over 1$ billion to bring a drug to market [37]. Compared to traditional drug development methods, drug repurposing technique is usually used to identify drugs for emerging and challenging diseases treatment based on approved or investigating existing drugs, which has the potential to significantly reduce development timelines and a large number of costs [38]. During the current COVID-19 pandemic, the drug repurposing is a very promising approach for discovering effective drugs from existing drugs to treat patients with COVID-19 [39]. There are three common strategies for finding drugs in terms of new use by drug repurposing method, including through serendipity, using experimental screening platforms, and computational methods [40]. The serendipity drug repurposing is based on specific pharmacological insights in the lab and clinic. The experimental method based drug repurposing is usually to bind assays to identify relevant target interactions using some techniques such as affinity

chromatography and mass spectrometry, which is costly and time-consuming [41]. Computational method based drug repurposing is mainly data-driven, which involves systematic analysis on multiple types of large-scale data such as gene expression, chemical structure, genotype or proteomic data or EHRs to acquire meaningful interpretations for repurposing hypotheses [40]. This method provides a great chance for identifying drugs quickly [42].

3.1 Computational drug repurposing

The methods of computational drug discovery can be roughly divided into two categories: Structure-based drug discovery and ML based drug discovery. Structure-based drug discovery is one of most popular methods in discovering antiviral drugs, which uses the technique of computational high-throughput ensemble docking and the binding affinities are obtained by physics-based equations [43]. The ML based drug discovery is to use ML techniques to obtain the representations of drugs or diseases, and then measure the similarities of these entities or build predictive models to obtain the relationships between drug and disease [36]. During COVID-19 pandemic, the process of simulations and docking in structure-based drug discovery need to be refined and repeated because there are multiple new experimental three-dimensional structures of the S protein and other viral targets [44]. Researchers have started to use ML techniques instead of structure-based drug discovery to predict drug binding and find candidate drugs due to the superiority of ML [45]. In ML based drug repurposing, the representation of structure of drug and disease is key for training ML models. Drug repurposing using regular and irregular data structure representations are discussed as follows. A general framework of ML based drug repurposing is demonstrated in **Figure 2**.

3.1.1 Drug repurposing on regular data structure

Regular data structures including vector, sequence, and matrix have been used for drug repurposing with different DL architectures [40]. In particular, for vector representation of drugs or diseases, a fully connected feedforward neural network (FNN) architecture is usually used to build a predictor or classifier [46]. In FNN, the input variables and output targets are connected by multiple layers with neurons. Each neuron from the preceding layer is connected to all neurons from the subsequent layer, and those connections are assigned different weights, which are trained and optimized through prediction loss and backpropagation. There are several FNN based drug repurposing studies [47-49] that profile data samples as vector representations. For example, Aliper et al. [47] used vector representations to build transcriptomic profiles for 678 different drugs, and then built a

FNN model to classify various drugs to therapeutic categories. The FNN model showed better performance compared to other computational methods such as naive Bayes, SVM, and RF. However, if the information of drug or disease is stored in the chemical image, using the FNN method is challenging because there would be a large number of weights in training FNN.

The matrix representation of drugs mainly refers to chemical images, which contain more molecular structure information. In this context, the advanced CNN [50], a preferred DL model specifically designed to obtain insights from those images, could be a promising approach to address the tasks. CNN is able to build relationships between the pixels in images and final predictive targets by multiple layers of nonlinear transformations [51]. A CNN typically consists of three layers: a convolution layer, a pooling layer, and a fully connected layer. CNN has been applied to explore drug function based on chemical images [52]. For example, Wallach et al. [53] used a CNN to build a predictive architecture, AtomNet, to predict molecular binding affinity to proteins, which obtained an AUC larger than 0.9 on 57.8% of the targets in the DUDE benchmark. Ragoza et al. [54] used CNN to build a protein-ligand scoring system to classify compound poses as binders or non-binders. A grid representation of protein–ligand structures was used as input of CNN model, which showed better discrimination than AutoDock Vina scoring [55] in terms of pose prediction and virtual screening.

In addition, some studies focused on modeling molecular sequence of drugs to identify new therapeutic implications. In this context, the recurrent neural networks (RNNs) [56], a kind of DL model for sequence data modeling, are usually involved. In a RNN, a recurrent neuron is used to address each element of a sequence at each timestamp, and integrates the historical information of the current element, which is obtained from the output of previous timestamp. There are several studies that used RNN to generate simplified molecular input line-entry system (SMILES) with desirable properties such as quantitative estimate of drug-likeness (QED) [57]. By fine tuning a pre-trained RNN, Olivecrona et al. [58] solved the issue in terms of a combination of handwritten rules for undesirable structure penalties. In addition, RNN architectures have been applied to generate focused molecule libraries for drug discovery by building sequence profiles for molecules based on SMILES codes [59]. Gao et al. [60] designed a hybrid of RNN and graph-based CNN model to identify drug-target interactions based on amino acids sequences and chemical structures.

3.1.2 Drug repurposing on irregular data structure

Irregular data structure based drug repurposing mainly involves network medicine [61-62] and graph representation learning [63]. Typically, a biomedical network or biomedical knowledge graph was first built. Then graph-based AI models, e.g., network embedding or deep graph neural networks, were used to learn low-dimensional representations for nodes and edges while preserving the graph structure. Finally, novel drug implication (e.g., potential drug-disease associations or drug-target interactions) discovery can be done by link prediction based on those representations [39, 64]. For example, Sosa et al. [65] built a large and heterogeneous knowledge graph, the Global Network of Biomedical Relationships (GNBR), including drug, disease, and gene (or protein) entities. They used graph embedding techniques to predict the links between drugs and diseases and obtained performance with 0.89 AUROC on a gold-standard test set. Zeng et al. [66] built a COVID-19 knowledge graph, CoV-KGE, to identify drug candidates for treating SARS-CoV-2 virus from 24 million Pubmed research articles. Amazon's AWS computing resources and graph embedding techniques were used on the built knowledge graph containing 15 million edges, 39 types of relationships among nodes including drugs, diseases, proteins/genes, pathways, and expression, and finally discovered 41 repurposable drugs such as tetrandrine, nadide, estradiol and so on. Some representative knowledge graph based studies are shown in **Table 2**.

3.2 Challenge and opportunities

Although computational drug repurposing has shown large potential for identifying effective drug candidates for treating COVID-19 infections, there remain challenges and opportunities for improving the efficiency of discovering drugs. In particular,

(1) Current dataset for computational drug discovery is very small. Although a gigantic collection GDB-17 has 166 billion compounds, it is only a tiny fragment of the chemical universe [67]. The ML methods may show poor performance when the model encounters compounds that the molecules have not been seen in train sets. The structure-based drug discovery needs accurate crystal structures to obtain better matching results in terms of proteins with drugs [45]. Building a larger and better dataset that contains more kinds of accurate crystal structures is beneficial for drug discovery, which may need more time, money and expertise.

(2) The Biomedical knowledge graph (BKG)-based approaches for drug development typically rely on quality of the BKG used. Different resources were used to build the BKGs in different projects, which may hence produce bias during discovering the promising repurposing drug candidates of COVID-19. There are efforts such as Heteionet [68] and our BKG [69] aiming at incorporating and harmonizing data

from diverse medical domains and resources to build comprehensive BKGs, however there is no golden standard to evaluate quality of them. This may limit reliability of the identified therapeutic implications.

(3) Computational data scientists need to work closely with chemists or doctors, which is very key. For example, extracting a broad range of properties of molecules based on domain knowledge from chemical experts is helpful for obtaining complete representation of molecules and then feeding them to ML models has the potential to improve model performance. When building a knowledge graph, some clinicians and medical school students may need manually reviewed clinical reports to aid model training, which may involve bias. More domain experts should work on them and the model developer should iteratively combine feedback from doctors who utilized the developed tool.

4. AI in COVID-19 Clinical Research

The studies of AI in COVID-19 clinical research can be roughly divided into two types (**Table 3**): the diagnostic and prognostic prediction of COVID-19 and the subphenotyping of COVID-19. For the former, researchers use ML techniques to build classifiers to identify or predict patients whether or not suffering from COVID-19 or different levels of severity of COVID-19. For the latter, researchers focus on using clustering methods to identify sub-groups, and furtherly investigate the different characteristics such as hospitalization, intensive services, and death of these sub-groups.

4.1 The diagnostic and prognostic prediction in COVID-19

Early and rapid identification of COVID-19 is urgently needed [70-71], which not only is important for immediate management and treatment of individual patient care but also provides guilds for public health in terms of patient isolation and COVID-19 containment [72]. A COVID-19 virus-specific reverse transcriptase polymerase chain reaction (RT–PCR) test is widely utilized to detect the COVID-19 disease [73]. However, this test usually takes up to two days to obtain final results, and serial tests may be considered to exclude the possibility of false negative results, which may underestimate the situation of COVID-19 pandemic and hinder government control in terms of disease transmission and healthcare workforce [72]. Recently, researchers have used data-driven methods to build classifiers with historical medical information for diagnosis or prediction. In particular, researchers have used image or non-image medical information to build classifiers. For image based studies, they trained classifiers with ML methods using extracted features from medical images, such as human lung CT scan images, chest X-ray, and ultrasound images, or use DL models to build classifiers on raw medical images. For non-image based studies, they extracted EHR information such as routine lab tests and integrated ML models to train a classifier or built a score system using selected predictors. A general framework of using AI techniques for COVID-19 patients' prediction is shown in **Figure 3.**

4.1.1 Image based predictive modeling in COVID-19

Three common types of images including CT image, chest X-ray, and ultrasound images are used to build classifiers to perform COVID-19 diagnosis. With a more accurate tool in CT scans, CT images usually contain more information that are useful for COVID-19 diagnosis [5]. Most previous CT image based studies mainly use CNN for COVID-19 diagnosis [5, 74-76]. For example, Xu et al. [74] used a CNN architecture to extract lung CT image spatial features from 618 CT images for diagnosing COVID-19, influenza-A viral pneumonia and healthy cases. Although CT image is a valuable component for COVID-19 diagnosis, CT imaging usually takes more time than X-ray imaging and causes more harm for patients because of more exposure to radiation. In addition, compared to CT imaging machines, the equipment for X-ray is low cost and easy to operate, which attracted researchers' attention to COVID-19 diagnosis [77-80]. For example, Wang et al. [78] built a hybrid model with CNN and SVM for diagnosing COVID-19 on two datasets including 1,102 and 625 chest X-ray images, which obtained the 99.33% and 95.02% of accuracy, respectively. More recently, clinicians have found that lung ultrasound images can show higher sensitivity than chest X-ray in diagnosing pneumonia in some cases [81- 82]. Due to the characteristics of a more widely available, lower cost, more safe, and real-time ultrasound imaging technique, using lung ultrasound images for diagnosis of COVID-19 is obtaining attention [83-84]. Roy et al. [84] used lung ultrasound images to predict disease severity using a deep network by integrating spatial transformer networks and CNN, which showed accurate prediction and localization of COVID-19 imaging biomarkers. These previous studies with images mainly use DL techniques to extract spatial information and build classifiers, which need more samples for training classifiers to obtain best performance. Data augment techniques have been considered to deal with the lack of medical image for COVID-19 diagnosis [80, 85]. Loey et al. [85] used a GAN with deep transfer learning based data augmentation techniques to strengthen original 306 chest X-ray images to 8,100 images for COVID-19 detection.

4.1.2 Non-image based predictive modeling in COVID-19

Non-image based classification of COVID-19 focuses on using EHR information to diagnose COVID-19, which consists of two types of studies: score system based and ML based COVID-19 diagnosis. For the former, researchers seek to identify important predictors, assign to their scores, sum these scores and discriminate the severity of disease [86-87]. For example, Liang et al. [86] built a predictive risk score (COVID-GRAM) system, which included 10 important predictive factors that were screened from 72 potential predictors among epidemiological, clinical, laboratory, and imaging variables, to estimate the risk of

developing critical illness for patients with COVID-19 admitted to the hospital. One limitation of these studies is that more professional clinical knowledge or experience is needed for selecting important predictors. Recently, the latter method was widely used for COVID-19 diagnosis [73, 88-90]. Yang et al. [73] built a gradient boosting decision tree (GBDT) model to predict an individual's COVID-19 infection status using three demographic information (i.e., age, sex, race) and 27 routine lab tests, which obtained an AUC of 0.854. With the advance of DL and the availability of EHR information, the DL architectures are gaining more attention for diagnosing COVID-19. Liang et al. [91] built a feedforward neural network based DL survival model for predicting the risk of COVID-19 patients developing critical illness using 74 baseline clinical features at admission from 1,590 patients in 575 medical centers. The proposed model was validated on three separate cohorts including 1,393 patients and showed high concordance index of 0.890, 0.852, and 0.967, respectively.

4.2 The subphenotyping of patients with COVID-19

Clinical subphenotyping is to divide patients who share a phenotype into several clusters [92]. Patients in a same cluster have similar characteristics such as demographics, clinical characteristics, treatments, comorbidities, and outcomes, which differentiate the cluster from other clusters [93]. The identification of subphenotypes is helpful for understanding the pathophysiology of critical care syndromes and can lead to personalized treatment and management [94]. Recently, data-driven subphenotyping has been explored for multiple diseases such as sepsis [95], asthma and allergies [96]. A general framework of using AI techniques for subphenotyping patients is shown in **Figure 4**.

The studies of COVID-19 subphenotyping can be roughly divided into two categories including static subphenotyping and dynamic subphenotyping. For the former, the researchers first extract patient clinical variables presenting at admission to the emergency department, hospitalization, or ICU, and then use clustering methods such as hierarchical clustering method, consensus cluster analysis method, and self-organizing map (SOM) to identify clusters, and finally investigate the characteristics such as comorbidities and outcomes of these clusters [97-101]. For example, Su et al. [100] employed agglomerative hierarchical clustering model and 30 routinely clinical variables to identify 4 subphenotypes among 8,199 patients with COVID-19 and validated them on internal and external cohorts both with 3,519 patients. There were many differences among discovered subphenotypes in terms of demographics, clinical variables, comorbidities, clinical outcomes, and medication treatments. Li et al. [101] used a SOM method and identified 4 subphenotypes on 48 clinical variables from 398 patients. These 4 discovered

subphenotypes showed different characteristics. These static variable based subphenotyping studies mainly identify the short term subphenotypes, which may ignore the information in terms of progress of disease and treatment. Although previous studies have discovered several subphenotypes, due to the variable presentation to health care after developing symptoms and the evolution of organ failure in critical care [102], static assessments of COVID-19 may be incomplete.

For the dynamic subphenotyping, the researchers consider the trajectory of variables during a long term period such as 3 days and use trajectory based clustering methods such as dynamic time warping (DTW) [103] and group-based trajectory modeling (GBTM) to identify clusters [104]. For example, V. Bhavani et al. [104] used the dynamic trajectories of COVID-19 patient temperature to identify subphenotypes. The differential pattern of temperature change may provide cues to a varied underlying inflammatory response to infection. However, this study only used the trajectory of a single variable, which may ignore the influence from other organ dysfunction. To consider trajectory from multiple organ dysfunction can refine the understanding of the natural history of COVID-19 in response to standard of care treatment and define patterns of disease that may benefit from novel therapeutic strategies [105]. Su et al. [103] used the trajectory of sequential organ failure assessment that described dysfunctions in six organs including respiration, coagulation, liver, cardiovascular, central nervous system, renal, to identify subphenotypes among the critically ill patients with COVID-19. They discovered distinct worsening and recovering subphenotypes within different baseline severity strata. Compared to baseline severity of illness, demographics and comorbidities, dynamic inflammatory markers and ventilator variables showed much difference between worsening and recovering subphenotypes. These dynamic variable based subphenotyping studies consider the longitudinal variable trajectories and have demonstrated great promise to achieve unique insights into the multiorgan dysfunction.

4.3 Challenge and opportunities

Although clinical research including building predictive models and subphenotyping COVID-19 patients have been paid more attention and promising initial results have been obtained, there are some challenges or opportunities. Specifically,

(1) Most of the previous clinical research in COVID-19 mainly used structured information such as demographic, lab tests, vital signs, to build the representation of patients for ML modeling. Unstructured information such as clinical notes, the reports of CT scan images may contain more detailed information for COVID-19 diagnosis. For example, Obeid et al. [106] performed text information analysis based on patients' self-reported symptoms to predict COVID-19 infection risk by a word embedding-based CNN. The unstructured information can be used as complementary information for structured information [107]. Integrating structured and unstructured information has the potential to completely represent the patient and improve model performance. How to integrate these information still needs to be investigated by researchers.

(2) For COVID-19 subphenotyping studies, validating the discovered subphenotypes on external sites is very important. However, the distribution difference between derivation cohort and validation cohort such as the size of cohort or heterogeneity of risk factors may generate different subphenotypes. Designing a method to measure the discrepancy of distribution and integrating them into a ML model may make contributions for identifying subphenotypes.

(3) Current static variables based subphenotyping studies mainly identify subphenotypes for patients at admission to the emergency department or ICU. These discovered subphenotypes may be too early for those patients, which may ignore the progress of COVID-19. Choosing proper time such as the first 6 hours after admission for subphenotyping patients may be able to avoid premature phenotyping [95].

(4) Although dynamic based COVID-19 subphenotyping considered the longitudinal trajectories and has the potential to obtain comprehensive understanding in terms of the natural history of COVID-19, it is still challenging to set a proper time interval for extracting features and build a representation for each patient based on trajectory.

5. AI in COVID-19 on behavioral and social sciences

The outbreak of COVID-19 produced an impact on people's daily behavior. Several specific topics including information search behavior change, the impact of misinformation, psychosocial impacts, mobility network, and contact tracing have been investigated. In particular, for information search behavior change, researchers want to know what kinds of key information would be searched popularly by citizens during COVID-19 pandemic. For example, Bento et al. [108] investigated information-seeking responses to the first COVID-19 case public announcement in a state. They found more people searched information in terms of "coronavirus", "coronavirus symptoms", and "hand sanitizer" after the first case announcement, which increased by about 36% (95% CI: 27% - 44%) on the day immediately and fell back to the baseline level in less than a week or two. The information about community-level policies such as quarantine and personal health strategies such as grocery delivery were not paid more attention, which indicated the study period was relatively early in the epidemic and there were limited elaborate policies from public discourse.

Investigating the information search behavior change can help the government to take proper measures. However, there is a large amount of misinformation in terms of COVID-19, which may mislead people's decision [109-111]. Bursztyn et al. [112] discovered the relationship between misinformation and health outcomes based on the two most popular cable news shows including Hannity and Tucker Carlson Tonight in the United States. An epidemiological model was used to measure the magnitudes in terms of treatment effects, which highlighted the relevance of externalities. They found that misinformation on mass media had significant social consequences. In order to identify low credibility news, Zhou et al. [113] constructed a repository based on 2,029 articles from about 2,000 news publishers and 140,820 tweets, which included multiple types of information on coronavirus, such as textual, visual, temporal, and network information. Several ML method based predictive models were built for identifying fake news and obtained competitive performance.

Investigating social media furtherly can find the cues in terms of psychosocial impacts during COVID-19 [114-116]. Saha et al. [117] discovered the temporal and linguistic changes in symptomatic mental health and support expressions during the COVID-19 pandemic by comparing Twitter streaming posts collected in the year of 2020 and 2019. They found that there is a significant increase in terms of people's mental health symptoms and support expressions during the COVID-19 period. Linguistic analyses showed that people express more concerns in terms of the COVID-19 crisis. Zhang et al. [118] built a fusion classifier that integrated DL model, psychological text features, and demographic information to investigate the relationships between feature and depression signals. The proposed model demonstrated an accuracy of 78.9% and has been used to analyze the depression level of different groups of people on Twitter in terms of three US states (New York, California, and Florida). They found people in Florida had a substantially lower level of depression.

In addition, investigating the spread patterns of cases and tracking individuals' movement are useful for controlling the spread of COVID-19. Chang et al. [32] used a metapopulation susceptible-exposed-infectious-removed (SEIR) model based on fine-grained and dynamic mobility networks to investigate the spread of COVID-19 in 10 US metropolitan areas. The built SEIR model can fit real case trajectory and reveals that setting specific occupancy for different points of interests is more effective than uniformly restricting mobility. With the wide use of smartphones, developing apps can facilitate the tracking of individuals' movements. Ahmed et al. [119] introduced three different kinds of smartphone contact tracing apps based on different ways of using servers and storing data, including centralized, decentralized, and hybrid architecture contact tracing apps. These apps have been used to identify and trace all recent contacts of newly discovered infected individuals.

5.1 Challenge and opportunities

Although more and more researchers have paid attention to behavioral and social sciences during COVID-19 pandemic, there are some challenges or opportunities. Specifically,

(1) Bias of data source: most previous studies used social media data from multiple data sources such as different news publishers or Tweet posts. There may be bias for those news publishers. Identifying those biases and integrating them into the model may be helpful for detailed analysis. In addition, there are other types of data such

as image and video, which can be integrated with text information to provide more insights for the analysis of COVID-19.

(2) Data privacy for tracing apps: although current apps have used some techniques such as decentralized contact tracing to keep privacy, a fully decentralised architecture has not been proposed [119]. A technique of using a peer-to-peer network may facilitate privacy-preserving information sharing amongst the user-devices.

(3) Behavioral changes in different groups such as old and young groups may be different during COVID-19 pandemic [120]. Interesting findings may can be found if researchers perform more fine-grained analysis. The government would take proper measures to provide assistance for those who may suffer from severe health problems such as depression or anxiety in different groups.

(4) Most previous studies on behavioral changes mainly focused on patients with COVID-19. Currently, with more and more citizens who get vaccinated, investigating the changes of mental health problems after vaccination may be interesting.

6. Discussion: Existing challenges and potential future directions

In previous sections, we reviewed studies using AI to address the COVID-19 pandemic from epidemiology, therapeutics, clinical research, social and behavioral aspects, and discussed the potential challenges and opportunities for each kind of application. This section will discuss existing challenges, potential directions and open questions from a general perspective.

6.1 Model interpretation

Model interpretation is very important in the medical domain because model outputs (e.g., diagnosis) without reasonable reasons make no sense to clinicians [121]. Different types of models may need different types of explainability. Previous models for COVID-19 analysis can be divided into two types: models built on ML and non-ML techniques. For models built on non-ML techniques such as using risk scores, it is not very difficult to explain final results by investigating each risk variable and other related clinical EHR information, which can be seen as intrinsic interpretability [122]. For example, Liang et al. [86] built a predictive risk score (COVID-GRAM) system, which used 10 important factors from the

epidemiological, clinical, laboratory, and imaging variables, to estimate the risk of developing critical illness for patients with COVID-19 admitted to the hospital. When interpreting the COVID-GRAM, clinicians only check scores of specific variables among these 10 factors. In addition, clinicians may modify their assessment if they find some values of variables are obviously abnormal. Intrinsically interpretable models based on non-ML techniques can provide better interpretability for clinicians, however, building models based on risk factors is not easy because more professional knowledge is necessary for developers to choose important risk factors.

With a larger amount of EHR, more and more ML models have been used in clinical applications. For models based on ML techniques, the interpretability can be seen as post hoc interpretation [122]. There are two directions for obtaining interpretable ML modeling. One is to derive explainable tools that show the contribution of input features to the final output. Several explainable tools such as LIME [123] and Shapley Additive Explanation [124] have been developed to determine the feature contributions by assigning importance scores. Adding attention mechanisms to hidden layers in DL models can also contribute to model interpretability [125]. Another key aspect is to interpret complex models based on multiple relatively simple models. For example, outputting the results of each convolutional layer of CNN in identifying specific regions of an image may provide cues for explaining final output results [126]. In addition, considering different levels of explainability in different applications may be sensible [122]. For example, clinicians may be relatively comfortable utilizing black-box models for some specific clinical applications (e.g., image analysis) that clinicians can readily intervene in. On the other hand, applying the black-box model to address unexplored problems may cause less comfort for clinicians.

6.2 Model security

Though ML models have been widely used in COVID-19 related applications, increasing evidence has been found that existing ML models could be fooled by adversarial examples and hence hard to obtain desirable performance [127-128]. Adversarial examples are models' inputs that are intentionally designed to make a mistake such as misclassification for identifying COVID-19 cases on medical IoT (Internet of Things) devices, which may poison the learning or the inference processes and furtherly compromise the security of ML models [129]. Recently, adversarial examples have been one of the most popular research topics in ML communities [130]. Although some studies in terms of adversarial examples have been done, two directions may be necessary for investigating the detection and

defense mechanisms in terms of COVID-19 DL poisoning process. One is to employ blockchain techniques to address adversarial example attacks on COVID-19 applications. For example, Nassar et al. [131] utilized blockchain to save benign attributes and parameters of each DL model, and furtherly transfer them to explainable AI for high-level users to check whether a particular model is compromised or not. Another is to study transferable adversarial examples [132], which have the potential to show better defense mechanisms against inference and model poisoning. Additionally, applying real-world attacks to test DL models and using industry standards such as IBM Adversarial Robustness Toolbox (ART) [133] to estimate and defend DL models against adversarial threats should be encouraged.

6.3 Model bias

AI techniques have become more ubiquitous for users to make or assist decisions in multiple domains such as recruiting (screening job applicants), banking (credit ratings/loan approvals), and judiciary (recidivism risk assessments). However, bias concern has been paid more attention recently by researchers in terms of whether the learned scoring function in ML model can make fair decisions in those real-world applications [134]. The bias in ML can be seen as the phenomenon of observing results that the learned model is systematically prejudiced across different groups defined by sensitive variables such as race or gender [135]. The bias may give rise to discrimination for protected groups and lead policymakers to make unfair decisions in real-world applications [136]. Detecting the bias and reducing its likelihood in model design and execution would play more critical roles in creating a fair treatment for specific populations [137].

The bias in ML that may cause discrimination can be roughly divided into three types [138-139], including disparate treatment, disparate impact and disparate mistreatment. In order to better understand the different types of bias, we take an example (**Table 4**) in terms of a binary classification problem where the ML model learns whether a loan would be returned using n+1 attributes, of which Q is a sensitive variable such as the user's race. For disparate treatment, it can be detected if the changing of a user's predicted label depends on the changing of the sensitive variable. In terms of the above example, it means the learned algorithm predicts positive labels for repaying a loan for White user population and a negative one for a Black user population. Removing the sensitive variable during model training is a way to avoid the dependence on the sensitive variable. For disparate impact, it can be discovered if the fraction of positive (negative) labels for the different sensitive groups is different. In terms of the above example, it means more percentage of

Black people were classified as defaulters as compared to White people. Removing the sensitive variable from the dataset is not an excellent way to prevent the disparate impact because other related features such as zip code may cause this issue. Checking training dataset and making sure there is not much imbalance in terms of positive and negative samples may help prevent disparate impact. For disparate mistreatment , it can be detected if there is a difference in terms of the proportion of accurate labels for different sensitive groups [139]. This bias was found by Propublica in the Northpointe algorithm [140], which misclassified innocent Black defenders as reoffending at twice the rate as White people. Keeping the same percentages of accurate labels for all sensitive groups is useful for rectifying the mistreatment. The objective of ML is to optimize a cost function by minimizing the difference between function outputs and real results. Adding the constraints to the objective function by considering the above-mentioned bias can avoid discrimination. A trade-off between fairness and accuracy should be considered when adding constraints.

6.4 Privacy issue and model precision

Privacy concerns are very important in applications of ML for healthcare. The "differential privacy" technique has been used to ensure model and data privacy in a single dataset [141-142]. For example, Chaudhuri et al. [143] proposed differential private approaches to preserve parameters obtained from logistic regression model or support vector machines. However, it remains challenging for most AI models to address two issues: (1) more parameters to be safeguarded in DL models; (2) keeping privacy when integrating data from multiple sites. In order to keep balance between privacy and model precision, federated learning (FL) [144], a framework of constructing a central parameter server to train a global model based on the parameters from multiple local sites that store their own sensitive data, has attracted more attention and offer great promise when integrating fragmented healthcare data from multiple medical sites with privacy-protection. More recently, Swarm Learning (SL) [145], a decentralized ML framework that integrates edge computing, blockchain-based peer-to-peer networking and dynamic central coordinator, has been paid more attention. Warnat-Herresthal et al. [145] used the SL framework to perform predictions in terms of COVID-19, tuberculosis, leukaemia and lung pathologies to illustrate the feasibility of SL. Under the SL framework, a shared global model is trained with a dynamic central coordinator that aggregates parameters from local sites keeping their sensitive data. Blockchain-based peer-to-peer networking is used to keep parameters privacy during transferring. Thus, data and parameters obtain double protection in SL, which can go beyond FL in real-world applications. Although the performance of FL and SL models is usually better than the model trained on single local sites, there exists large room for improvement compared to the central model trained by aggregating data from all local

sites without any consideration of privacy. How to improve model performance is still an important problem. In addition, most applications using the FL and SW framework mainly focus on disease risk prediction that is relatively simple. Employing these models for more complex applications such as medical treatment and providing medication prescripts may be more worth exploring.

7. Conclusion

In this study, we reviewed existing studies on using AI techniques to deal with COVID-19 pandemic related problems from four aspects including epidemiology, therapeutics, clinical research, social and behavioral studies. All the results available in those previous literature demonstrated the applicability and great promise of AI in addressing COVID-19 pandemic. Also, some challenges, directions, and open questions are provided in this review, which may be helpful for researchers to explore more related topics.

Author contributions

Fei Wang planned and structured the whole paper. Zhenxing Xu and Chang Su conducted the literature review and drafted the manuscript. Zhenxing Xu, Chang Su, Yunyu Xiao and Fei Wang. reviewed and edited the manuscript.

Funding

The research was supported by NSF 1750326, 2027970, NIH RF1AG072449, R01MH124740, as well as Amazon AWS Machine Learning for Research Award and Google Faculty Research Award. The work is also supported by Gates Foundation CORONAVIRUSHUB-D-21-00125.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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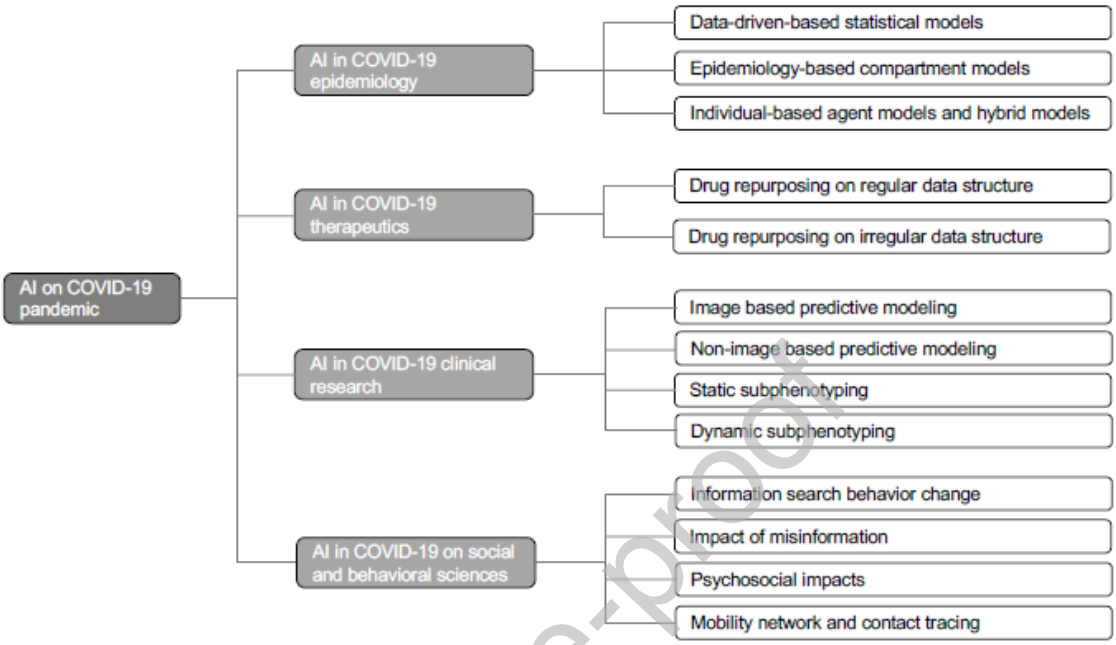

Figure 1: The overall framework of this review. We review four aspects (i.e., epidemiology, therapeutics, clinical research, social and behavioral studies) in terms of applications of AI on COVID-19 pandemic. Also the challenges of each aspect are provided. Finally, the general challenges, directions, and open questions are discussed on model interpretation, model security, model bias, privacy issue and model precision.

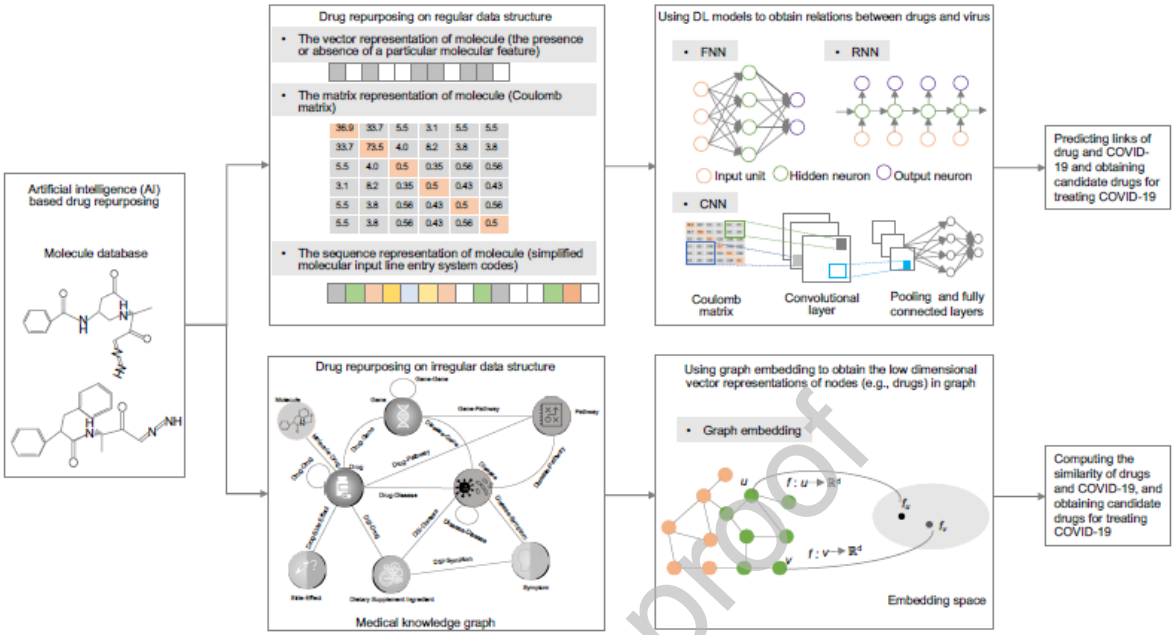

Figure 2. A general framework of ML (machine learning) and DL (deep learning) based drug repurposing. FNN: feedforward neural network; CNN: convolutional neural network; RNN: Recurrent neural network.

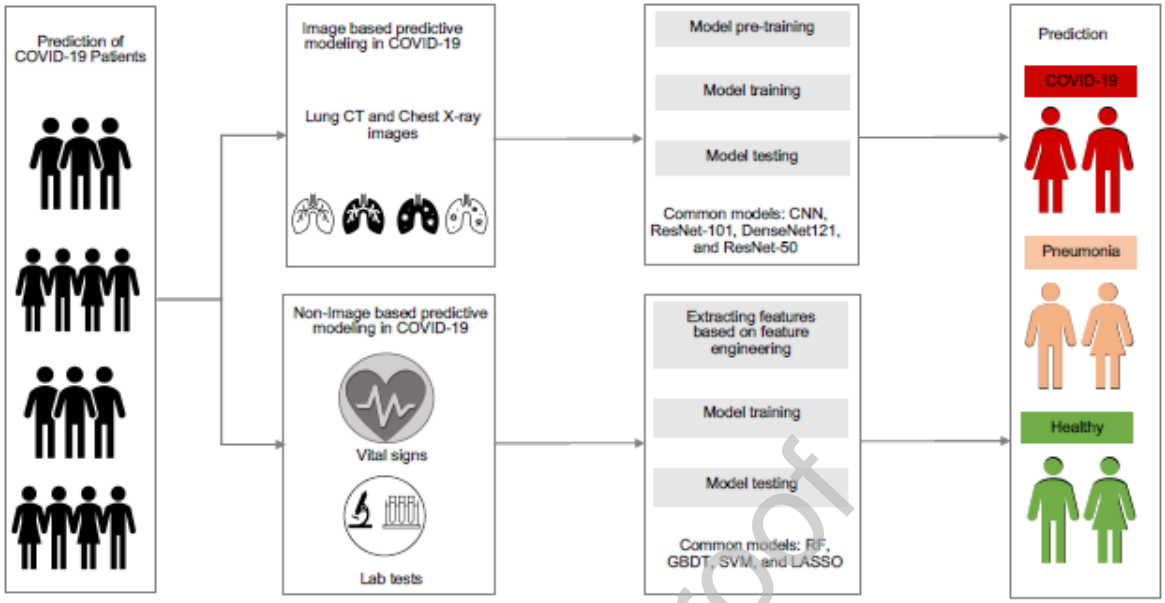

Figure 3. A general framework of using ML (machine learning) and DL (deep learning) techniques in COVID-19 diagnostic and prognostic prediction.

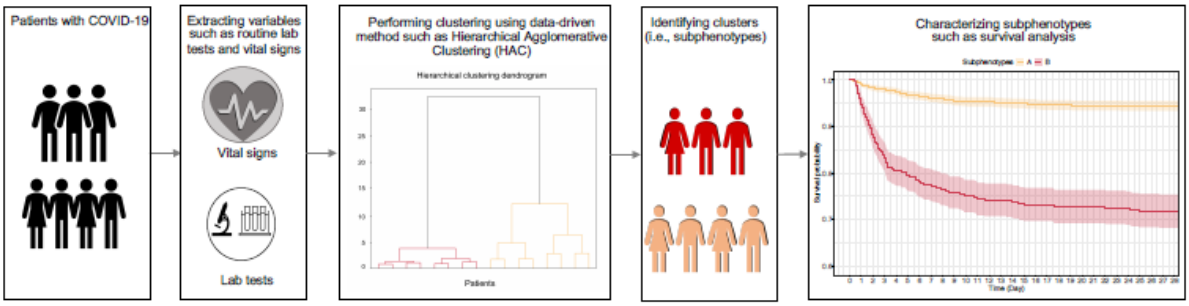

Figure 4. A general framework of using AI techniques for the subphenotyping of patients with COVID-19. SOM: Self-Organizing Map; HAC: Hierarchical Agglomerative Clustering.

Table 1. The summary of studies in terms of the applications of AI in epidemiology

Reference (Author, Month, Year)	Task	Data Source & Size	Model	Result
Parbat et al. (May 2020) [15]	predict the total number of deaths, recovered cases, cumulative number of confirmed cases, and number of daily cases.	Johns Hopkins Github repository (https://github.com/CSSEGISandData/COVID-19) between 01/03/2020–30/04/2020 cases:35043 deaths:1147 recovered patients:8889.	support vector regression model	The proposed model was efficient and has higher accuracy (more than 87%) than linear or polynomial regression methods.
Zeynep Ceylan (April 2020) [146]	estimate the prevalence of COVID-19 in Italy, Spain, and France.	The data of COVID-19 collected from the WHO website (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/) between 21/02/2020–15/04/2020 Italy: mean prevalence case 57,262, mean incidence case 3009; Spain: mean prevalence case 54,075, mean incidence case 3521; France: mean prevalence case 30,233, mean incidence case 2092.	Auto-Regressive Integrated Moving Average (ARIMA) model	ARIMA (0,2,1), ARIMA (1,2,0), and ARIMA (0,2,1) showed the best prediction performance (more than 82% accuracy) for Italy,

				Spain, and France, respectively.
Benvenuto et al. (February 2020) [147]	predict the epidemiological trend of the prevalence and incidence of COVID-2019	the Johns Hopkins epidemiological data (https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html)	Auto-Regressive Integrated Moving Average (ARIMA) model	ARIMA (1,0,4) and ARIMA (1,0,3) showed the best performance in terms of determining the prevalence and incidence of COVID-2019, respectively.
Rodriguez et al. (September 2020) [148]	real-time COVID-19 forecasting including Incidence and cumulative weekly deaths and Incidence daily hospitalizations.	Johns Hopkins University (JHU) COVID Tracking Project (https://covidtracking.com)	DeepCOVID including data module, prediction module, and explainability module based on deep learning model	The proposed model was used in CDC COVID-19 Forecast Hub (since April 2020).
Singh et al. (September 2020) [149]	predict the spread of COVID-19	Data collected from Kaggle website (https://www.kaggle.com/imdevskp/covid19-corona-virus-india-dataset)	Random Forest and Kalman Filter	The proposed model showed good perform

		Data covered 15 States of India.		ance in terms of short-term estimation, but not so good for long-term forecasting.
Zheng et al. (July 2020) [24]	predict the development and spread of the COVID-19	Data collected from the national and provincial health commissions, and dxy.com website (Real-time data API for COVID-19 epidemic) (https://lab.isaaclin.cn/nCoV/zh)	Hybrid AI Model based on susceptible-infected (ISI) model and RNN model	The proposed model acquired the lower mean absolute percentage errors in Wuhan (0.52%), Beijing (0.38%), Shanghai (0.38%), and country wide (0.86%) for the next 6 days.
Huang et al. (May 2021) [22]	forecast the trend of COVID-19 pandemics under the influence	hospitalization and cumulative morality of COVID-19. Houston, Texas, May 1, 2020 -- June 29, 2020	risk-stratified SIR-HCD	The proposed model obtained lower mean squared error (MSE)

	of reopening policies.			and higher prediction accuracy compared to other models, and supports counterfactual analysis.
Liu et al. (May 2021) [150]	investigate the influence (reproduction number) of non-pharmaceutical public health interventions on COVID-19 epidemics in the United States	COVID Tracking Project (https://covidtracking.com)	a generalized linear model (GLM)	Different NPIs showed different levels of reproduction numbers. The stay-at-home played the most important role and contributed approximately 51% (95% CI 46%-57%). The gathering ban (more than 50 people) was not

				very important, which only contributed 7% (2%-11%).
Tian et al. (July 2020) [151]	compare the effect of mild interventions in Shenzhen and countries in the United States	daily cumulative confirmed cases of COVID-19 in Shenzhen, China and the countries in the United States (https://github.com/CSSEGISandData/COVID-19)	a synthetic control method with a modified selection of control variables and the proposed SIHR model	Implementing the early mild interventions has the potential to subdue the epidemic of COVID-19.
Zou et al. (May 2020) [23]	forecast the spread of COVID-19	the Johns Hopkins University Center for Systems Science and Engineering; The New York Times data; The data from most states between 03/22/2020 and 05/10/2020. More than 40,000 cases.	SuEIR model	The proposed model has been adopted by the CDC for COVID-19 death forecasts.
Friedman et al. (May 2021) [152]	predict mortality of patients with COVID-19	Public data: https://github.com/pyliu47/covidcompare.	SEIR model, Dynamic Growth, SIKJalpha.	Seven predictive models that showed better perform

				ance which had a median absolute percent error of 7 to 13% at six weeks.
Murray et al. (March 2020) [153]	Predict hospital bed-days, ICU-days, ventilator-days and deaths	Data from local government, national government, and WHO websites were used.	A statistical model based on parametrized Gaussian error function	They forecasted total beds (64,175), ICU beds (17,380), ventilators (19,481), deaths (81,114) at the peak of COVID-19 in the United States between March to June 2020.
Hsiang et al. (September 2020) [154]	investigate the effect (rate of transmission) of non-pharmaceutical public health intervent	COVID-19 data collected from government reports, policy briefings and news articles (https://github.com/bolliger32/gpl-covid)	reduced-form econometric model	The proposed model showed the interventions can reduce the rate of transmi

	ions on COVID-19 epidemics in China, South Korea, Italy, Iran, France and the United States			ssion and delay on the order of 61 million confirmed cases across 6 countries.
Li et al. (January 2021) [155]	predict the epidemic trends in terms of future confirmed cases within 7 days	Coronavirus Update (Live): (https://www.worldometers.info/coronavirus/) Coronavirus (COVID-19) Lockdown Tracker	Aura Vision. (https://auravision.ai/covid19-lockdown-tracker/) List of countries and dependencies by population: (https://en.wikipedia.org/w/index.php?title=List_of_countries_and_dependencies_by_population&oldid=960653268)	a transfer learning method called ALeRT-COVID using attention-based RNN architecture	ALeRT-COVID obtained a higher prediction in terms of future confirmed cases
Wang et al. (May 2021) [156]	investigate the impact of the temperature and relative humidity on effective reproductive number in COVID-19 epidemics	Records of 69,498 patients from Chinese National Notifiable Disease Reporting System and 740,843 confirmed cases from COVID-19 database of JHU CSSE (https://github.com/CSSEGISandData/COVID-19/).		Fama-Macbeth Regression [35]	High temperature and humidity can make contributions to the reduction of the transmission of COVID-19.
Rockett et al.	revealing COVID-19	data collected from infected patients during the first 10 weeks of COVID-19 containment in Australia, which reported by New South Wales (NSW) Ministry of Health		agent-based model	The predictions

(July 2020) [25]	transmission in Australia			from ABM were concordant with the local transmission rates.
Alzu'bi et al. (December 2020) [26]	investigate the effect of non-pharmaceutical public health interventions on COVID-19 epidemics	Coronavirus data collected from two urban neighborhoods separated by crossings. 1000 persons.	agent-based model by extending the SIR model	The policies including staying home and hospital isolation policies, and preventing travel between cities made contributions to the reduction of the prevalence and the deaths.
Brauer et al. (May 2021) [157]	estimated global access to handwashing with soap and water	Observational surveys in the context of the Global Burden of Diseases, Injuries, and Risk Factors Study in terms of access to a handwashing station with available soap and water for 1,062 locations from 1990 to 2019.	spatiotemporal Gaussian process regression modeling	The handwashing access should be considered when building the forecast

				ing models of COVID-19 in terms of low-income countie s.
Jr et al. (Octo ber 2020) [158]	investiga te the effect of social distancin g mandate s and levels of mask use	COVID-19 case and mortality data from 1 February 2020 to 21 September 2020 in the United States	SEIR model	Keeping univers al mask use was enough to relieve the worst effects of epidemi c resurge nces in multipl e states in the United States. Keeping social distanci ng was helpful for reducin g the number of deaths for patients with COVID-19.

Table 2. The summary of studies in terms of the applications of AI in drug repurposing

Reference (Author, Month, Year)	Method	Data Source & Size	Number of Identified drug candidates	Identified drug candidates
Zhou et al. (March 2020) [159]	Network-based method (drug–target network; human protein–protein interaction network)	DrugBank database (v4.3), Therapeutic Target Database (TTD), PharmGKB database, ChEMBL (Sv20), BindingDB, and IUPHAR/BPS Guide to PHARMACOLOGY. And other 18 bioinformatics and systems biology databases including 351,444 unique PPIs (edges or links) connecting 17,706 proteins (nodes).	16 drug candidates and 3 drug combinations	Candidates: Irbesartan; Toremifene; Camphor; Equilin; Mesalazine; Mercaptopurine; Paroxetine; Sirolimus; Carvedilol; Colchicine; Dactinomycin; Melatonin; Quinacrine; Eplerenone; Emodin; Oxymetholone. Combinations: sirolimus plus dactinomycin, mercaptopurine plus melatonin, and toremifene plus emodin.
Zeng et al. (July 2020) [66]	Knowledge-graph and deep learning	24 million Pubmed research articles. A built knowledge graph contains 15 million edges, 39 types of relationships among nodes including drugs, diseases, proteins/genes, pathways, and expression.	41	Tetrandrine, Nadide, Estradiol, and so on (see Table 1 of this reference)
Gysi et al. (May 2021) [62]	Network-based method including network proximity,	21 public databases for compiling protein-protein interactions (PPI) data including 18,505 proteins and 327,924 interactions between them; DrugBank database for obtaining drug-	4	Auranofin, Azelastine, Digoxin, and Vinblastine.

	network diffusion, and AI-Net	target information including 26,167 interactions between 7,591 drugs and their 4,187 targets.		
Wang et al. (May 2021) [160]	Knowledge-graph and deep learning	25,534 peer-reviewed scientific articles	41	Connecting 41 drugs based on Benazepril, Losartan, and Amodiaquine.
Zhang et al. (February 2021) [161]	Knowledge-graph and deep learning	PubMed, LitCovid,CORD-19. The built knowledge graph has 131,355 nodes and 2,558,935 relations.	5	Paclitaxel, SB 203580, Alpha 2-antiplasmin, Metoclopramide, and Oxymatrine.
Gordon et al. (April 2020) [162]	Network-based method	Public sources such as An interactive protein–protein interaction map https://kroganlab.ucsf.edu/network-maps; databases such as ChEMBL [PMID: 27899562], ZINC[PMID: 26479676] and IUPHAR/BPS Guide to Pharmacology [PMID: 31691834].	69	Silmitasertib, Bafilomycin A1, Haloperidol, Loratadine, Entacapone, and so on.(see Supplementary Tables 5 and 6 of this reference)
Beck et al. (March 2020) [163]	Knowledge-graph and deep learning	Drug Target Common (DTC) database and BindingDB database.	5	Atazanavir, Remdesivir , Efavirenz, Ritonavir, and Dolutegravir.
Mall et al. (July 2020) [164]	Knowledge-graph and deep learning	MOSES, ChEMBL, UniProt, PubChem and NCBI.	19	Remdesivir, lopinavir, Ritonavir, and Hydroxychloroquine (see Table 3 of this reference)

Table 3. The summary of studies in terms of the applications of AI in clinical research

Reference (Author, Month, Year)	Task	Data source & Size	Method	Results
Su et al. (March 2021) [165]	Explore albumin level between patients with COVID-19 and patients with sepsis.	308 patients with COVID-19 and 363 patients with Sepsis	Chow's test, linear mixed-effects models, Fisher's exact test, t-test, and Wilcoxon rank-sum test	Two phases of alterations in albumin levels for patients with COVID-19 were found, which were not presented with patients with sepsis.
Liang et al. (May 2021) [86]	Estimate the risk of developing critical illness for patients with COVID-19	72 potential predictors were considered from 1590 patients with COVID-19 in the 575 hospitals of 31 provincial administrative regions in China as of January 31, 2020.	Least Absolute Shrinkage and Selection Operator (LASSO) and Logistic Regression (LR) models	AUC=0.88 (95% CI, 0.84-0.93) on a validation cohort with 710 patients.
Burn et al. (October 2020) [166]	Explore the characteristics of patients with COVID-19 and influenza	34,128 adult patients with COVID-19 and 84,585 patients with influenza (US: 8362, South Korea: 7341, Spain: 18,425)	Data-driven approach	Compared to patients with influenza, patients with COVID-19 were more male, younger, and with fewer comorbidities and lower medication use.
Roth et al. (May 2021) [167]	Investigate the characteristics of patients with COVID-19 in terms of in-hospital mortality in the United	20736 adults with a diagnosis of COVID-19 in the US between March and November 2020.	A multiple mixed-effects logistic regression	The mortality rates for patients with COVID-19 were different between the months of March and April and later months in 2020, which were not fully explained by changes in age, sex,

	States			comorbidities, and disease severity.
Williams et al. (May 2021) [87]	Predict hospitalization, intensive services, and death for patients with COVID-19	The cohort for model development has More than 2 million patients diagnosed with influenza or flu-like symptoms any time prior to 2020. The cohort for model validation included 43,061 COVID-19 patients form South Korea, Spain and the United States.	Data-driven approach	The ranges of AUC on validation in terms of three outcomes including hospitalization, intensive services, and death were 0.73-0.81, 0.73-0.91, and 0.82-0.90, respectively.
Liang et al. (July 2020) [91]	Predict the risk of COVID-19 patients developing critical illness	74 baseline clinical features at admission from 1590 patients with COVID-19 in the 575 hospitals of 31 provincial administrative regions in China as of January 31, 2020.	Feedforward neural network.	The proposed model was validated on three separate cohorts including 1,393 patients and showed the concordance index of 0.890, 0.852, and 0.967, respectively.
Yang et al. (December 2020) [168]	Investigate population drifting in terms of COVID-19 patients	21 routine blood tests from 5,785 patients in ED of New York Presbyterian Hospital/Weill Cornell Medical Center (NYPH/WCMC) between March 11 and June 30,2020.	Density-based spatial clustering of applications with noise (DBSCAN) and the Unified manifold approximation and projection (UMAP), t-test, Fisher's exact test.	The number of SARS-CoV-2 patients with the COVID-19 HRP became less and less from March to June 2020.
Zhang et al. (June 2020) [5]	Diagnose COVID-19	532,506 human lung CT scan images from 3,777 patients, China Consortium of Chest CT	CNN	Internal validation: accuracy=92.49%; External validation:

		Image Investigation (CC-CCII)		accuracy=90.70%.
Wang et al. (May 2020) [76]	Diagnose COVID-19	lung CT images: 5,372 patients from seven cities or provinces in China.	A fully automatic DL model (DenseNet121-FPN)	AUC 0.87 and 0.88 on two validation sets in distinguishing COVID-19 from other pneumonia and AUC 0.86 in distinguishing COVID-19 from viral pneumonia.
Ozturk et al. (June 2020) [79]	Diagnose COVID-19	X-ray images: 127 COVID-19 cases, 500 no-finding, 500 pneumonia. The Cohen JP and the ChestX-ray8 databases	CNN	An accuracy of 98.08% for classifying COVID-19 and No-findings and 87.02% for classifying COVID-19, No-findings, and Pneumonia.
Chen et al. (October 2020) [88]	Predict the severity of COVID-19	52 features from 362 patients with COVID-19 including 214 non-severe and148 severe in China.	RF	95% accuracy when considering all features and 99% accuracy when only using top 10 important features selected by Gini impurity.
Xu et al. (October 2020) [74]	Diagnose COVID-19	618 CT images in total. 219 samples from 110 patients with COVID-19; 224 samples from 224 patients with IAVP; 175 samples from 175 healthy cases. These samples are from China.	CNN	Accuracy = 86.7%
Avila et al. (June 2020)	Predict COVID-19	510 patients including 73 positives for COVID-	Gaussian Naïve	100% sensitivity and 22.6% specificity, 76.7%

[89]		19 and 437 negatives were from the emergency department of Hospital Israelita Albert Einstein (HIAE, São Paulo, Brazil).	Bayes (NB)	for both sensitivity and specificity, and 0% sensitivity and 100% specificity when prior values were set to 0.9999, 0.2933, 0.001, respectively.
An et al. (October 2020) [90]	Predict mortality for patients with COVID-19	sociodemographic and medical information from 10,237 patients with COVID-19 in a nationwide Korean cohort.	LASSO, SVM and RF	The LASSO model obtained best AUC (0.962 [0.945, 0.979]), and identified several significant predictors such as old age and preexisting DM or cancer.
Mei et al. (May 2020) [72]	Diagnose COVID-19	CT scan images and non-image information such as demographic and laboratory tests from 905 patients between 17 January 2020 and 3 March 2020 from 18 medical centers in 13 provinces in China.	CNN+MLP	AUC=0.92 on a test set with 279 patients.
Ardakani et al. (June 2020) [75]	Diagnose COVID-19	1,020 CT images from 108 patients in Iran University of Medical Sciences (IUMS) hospital.	CNN (ResNet-101)	AUC = 0.994, Sensitivity = 100%, Specificity = 99.02%, Accuracy = 99.51%.
Yang et al. (November 2020) [73]	Predict COVID-19	Demographic information (i.e., age, sex, race) and 27 routine lab tests from 3,356 SARS-CoV-2 RT-PCR tested patients.	Gradient boosting decision tree (GBDT)	AUC=0.854 (95% CI: 0.829-0.878).

		These tests were from NYPH/WCM dataset.		
Roy et al. (August 2020) [84]	Diagnose COVID-19	Italian COVID-19 Lung Ultrasound DataBase: 277 lung ultrasound videos from 35 patients, corresponding to 58,924 images.	Spatial Transformer Networks and CNN	Accurate prediction and localization of COVID-19 imaging biomarkers in three tasks including frame-based classification, video-level grading and pathological artifact segmentation.
Narin et al. (May 2020) [77]	Diagnose COVID-19	341 images from COVID-19 patients, 2800 normal chest images, 1493 viral pneumonia and 2772 bacterial chest X-ray images	CNN	96.1%, 99.5%, and 99.7% accuracy on three datasets, respectively.
Jain et al. (September 2020) [80]	Diagnose COVID-19	1,832 X-ray images strengthened from original 1,215 X-ray images by using data augmentation techniques	CNN (ResNet-50)	Training-validation-testing: accuracy, recall, and precision were 99.77%, 97.14%, and 97.14%, respectively. 5-fold cross validation: average accuracy, sensitivity, specificity, precision, and F1-score were 98.93%, 98.93%, 98.66%, 96.39%, and 98.15%, respectively.
Wang et al. (November 2020) [78]	Diagnose COVID-19	two datasets including 1,102 and 625 chest X-ray images, respectively.	CNN and SVM	99.33%, and 95.02% accuracy on two datasets, respectively.
Loey et al. (April 2020) [85]	Detect COVID-19	8100 chest X-ray images strengthened from original 306 chest X-ray images by using data augmentation	GAN with deep transfer learning	Testing sets: 100% accuracy; Validation set: 99.9%

		techniques.		accuracy.
Li et al. (September 2020) [101]	Diagnose COVID-19; Identify subphenotypes	Public dataset: 413 patients with COVID-19 and 1071 patients with influenza	XGBoost model; a self-organizing map (SOM)	Sensitivity = 92.5%; Specificity = 97.9%; Identified 4 subphenotypes which showed much difference in terms of gender distribution and levels of CRP and serum immune cells.
Zhou et al. (April 2020) [169]	Identify subphenotypes	Mexican Government COVID-19 open data including 778,692 COVID-19 patients.	meta-clustering technique	Identify 3 clusters which showed different recovery rates
Su et al. (July 2020) [103]	Identify subphenotypes	NYP-WCMC eligible 318 patients extracted from 1661 patients with COVID-19 and NYP-LMH eligible 84 patients extracted from 458 patients with COVID-19.	Dynamic time warping and hierarchical agglomerative clustering method	Discovered distinct worsening and recovering subphenotypes within three strata including mild, intermediate, and severe strata.
V.Bhavani (December 2020) [104]	Identify subphenotypes	696 hospitalized patients in University of Chicago Medicine	Group-based trajectory modeling (GBTM)	Discovered 4 subphenotypes which were different in experiencing cytokine storm, coagulopathy, and cardiac and renal injury.
Lascarrou et al. (March 2021) [98]	Identify subphenotypes	416 COVID-19 patients with moderate to severe ARDS at 21 intensive care units in Belgium and France.	Hierarchical clustering method	Identified 3 subphenotypes which have different characteristics on comorbidities, mortality, sex, the duration of symptoms, plateau and

				driving pressure.
Legrand et al. (October 2020) [97]	Identify subphenotypes	608 patients in at eight teaching hospitals of the Assistance Pub- lique-Hôpitaux de Paris	Consensus cluster analysis method	Identified 3 subphenotypes which are different in terms of a history of chronic hypertension, the presence of fever, respiratory and non-respiratory symptoms, and age.
Schinkel et al. (February 2021) [99]	Identify subphenotypes	2019 patients collected from COVID Predict project in the Netherlands.	Consensus cluster analysis method	Identified 3 subphenotypes which showed much difference in terms of demographics, comorbidities, and clinical outcomes.
Su et al. (July 2021) [100]	Identify subphenotypes	Development cohort with 8199 patients and internal and external validation cohorts both with 3519 patients. Those patients were from five major medical centers in New York City (NYC), between March 1 and June 12, 2020.	Data-driven (agglomerative hierarchical clustering model)	Identified 4 subphenotypes which showed much difference in terms of demographics, clinical variables, comorbidities, clinical outcomes, and medication treatments

Table 4. An example of a binary classification problem based on ML in terms of whether a loan would be returned using n+1 attributes (Q is a sensitive variable such as the user's race). Labels “0” and “1” represent “Returned” and “defaulted”, respectively.

	Variable_1	Variable_2	...	Variable_n	Q (sensitive variable)	Label (Y)
Client_1	F11	F12	...	F1n	Q1	1
Client_2	F21	F22	...	F2n	Q2	0
...	...	...	...	...	...	...
Client_m	Fm1	Fm2	...	Fmn	Qm	1

Graphical abstract